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08/466,698	06/06/95	SANSONETTI	P 2356.0043-02

EXAMINER	
CAPUTA, A	
ART UNIT	**PAPER NUMBER**
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DATE MAILED: 10/31/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☒ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-12 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-12 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☒ been received ☐ not been received ☒ been filed in parent application, serial no. 07/460,946; filed on 3/24/90.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

Specification

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

2. The use of the trademarks such as RPMI 1640 (see page 13) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

3. References cited in the specification but not cited in compliance with 37 CFR 1.98 have not been considered. If applicants desire specific references to be considered and/or made of the record then applicants should provide copies of these references and comply with the conditions of 37 CFR 1.56 and 1.97-1.99, including a completion of PTO-1449. See also MPEP 609, MPEP 707.05(b), and MPEP 2001.06 through 2004.

Claim Rejections - 35 USC § 112 2nd paragraph

4. Claims 1-12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-12 are vague and indefinite in the recitation of "substantially" and "substantial". It is not clear what constitutes as "substantially" or "substantial"?

b. Claims 1-12 are vague and indefinite for use of the term "characterized" because said term can be interpreted as an improvement over an old method.

Claim Rejections - 35 USC § 112/1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one of ordinary skill in the art how to make and/or use the claimed invention, i.e. failing to provide an enabling disclosure.

a. The specification fails to provide substantive guidance of how to use the claimed modified Shigella as a vaccine, particularly since no animals were immunized with modified strains of Shigella and subsequently challenged with the wild type Shigella. Furthermore, the specification provides sufficient guidance of using the animal model to predict the use in humans. As exemplified in the art, Sansonetti et al. (Vaccine 9: 416-422 6/91) states "We believe that the macaque model provides indications but no definitive answers on the suitability of a given strain for human vaccination". Furthermore Sansonetti et al. teaches that it is not clear to safety of the double mutant SC5700 (i.e. *icsA*$^-$, iuc$^-$) in humans since human beings are more sensitive to a much smaller inoculum of Shigella (see page 448, last full paragraph) and Fontaine et al., Infection and Immunity 56(12):3099-3109 1988) states "To what extent these observations in cellular and animal models can be applied to human shigellosis is of course a major question" (see page 3108, last paragraph). Accordingly, it is unpredictable and would be undue burden for a skilled artisan to determine using the claimed *Shigella* as a vaccine.

b. It is apparent that numerous modified Shigella are required to practice the claimed invention. That is, one skilled in the art can not make the claimed microorganisms or vaccines without the Shigella species which contain the claimed inactivated genes. Accordingly as a required element, the modified Shigella must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available the enable requirements of 35 U.S.C. § 112, first paragraph may be satisfied by the deposit of the claimed microorganisms and limiting the claims to the deposited mutants. See 37 C.F.R 1.802.

In the instant case the construction of claimed Shigella mutants requires knowledge of the nucleotide sequence of said genes, which regions are responsible for biological activity, and the number of nucleotides which must be deleted or inserted. Due to the limited teaching of the specification and the unpredictable nature of which mutations are useful one skilled in the art can not practice the invention as claimed absent undue experimentation. In view of the foregoing the only means by which applicants can provide an enabling disclosure for the Shigella mutants is by depositing said mutants and limiting the claims to the deposited mutants.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete

name and full street address of the depository is required. As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;
2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if the test is not done by the depository; and
7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the Shigella mutants described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

6. Claims 1-13 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

> Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

9. Claim 13 is rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Sekizaki et al. (Infection and Immunity 55(9):2208-2214 1987)

Sekizaki et al. teach of Shigella mutants which lost the ability to produce high levels of Shiga toxin (see abstract and page 2212). Sekizaki et al. does not characterize the Shigella mutant as claimed. Nevertheless it is reasonable for one of ordinary skill in the art to conclude the mutant strain as claimed is the same or an obvious or analogous variant as the mutant strains as set forth by Sekizaki et al. since they have the same functional properties (i.e. Shigella mutant which has lost the ability to produce high levels of Shiga toxin).

Applicants are advised that since the Office does not have the facilities for examining and comparing applicant's product with the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the product of the prior art does not possess the same material structural and functional

characteristics of the claimed product). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

10. Claims 1-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Mills et al. in view of Sekizaki et al., Nassif et al., Makino et al., and Ozenberger et al.

Mills et al. teach the attenuation of Shigella can be achieved by loss of, or deletion of genes from the large virulence plasmid that specifies bacterial invasion as well as site directed inactivation of the toxin gene. Mills et al. teaches the potential for reversion to virulence represent possible problems (see last paragraph).

Mills et al. and Sekizaki et al. both teach of methods of replacing the Shigella toxin gene with a mutant allele. Sekizaki et al. suggests that toxin production is hazardous.

Ozenberger et al. teaches of using methods of insertion and deletions of the siderophore gene enterobactin to impair the ability to grow.

Nassif et al. teaches that Shigella flexerni mutant which no longer produces the siderophore aerobactin displays altered extracellular growth capacity. Nassif et al. teaches it would not be expected to provide sufficient attenuation, but it would certainly be considered additional security (see last paragraph).

Makino et al. disclose a region on the large virulence plasmid of Shigella (the virG gene) is required for cell-cell spread and is involved in the pathogenesis of Shigella. Makino et al. teaches that the mutant may be a plausible candidate for a vaccine (see page 554, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate into the method of attenuating Shigella by inactivating genes required for bacterial invasion and/or Shigella toxin as described by Mills

and Sekizaki et al., inactivation of the gene required for aerobactin as taught by Nassif et al. and the inactivation of the gene required for cell-cell spread (virG) as taught by Makino et al. using methods of allelic exchange and/or deletion mutagenesis as taught by Mills, Sekizaki et al, or Ozenberger et al. for the expected benefit of developing a vaccine since as described by Sekizaki et al. toxin production is a hazard in a vaccine, virG and aerobactin are useful in a vaccine (see Nassif et al. and Makino et al.) and aerobactin mutant provides additional security for sufficient attenuation in a vaccine (see Mills et al. and Nassif et al.).

Thus the claimed invention as a whole is clearly prima facie obvious, in the absence of evidence to the contrary.

11. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 13 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 39 of copending application Serial No. 08/118,100. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to *Shigella* mutant which has an inactivated Shiga toxin gene (Shiga-toxin A).

This is a *provisional* obviousness-type double patenting rejection.

12. Any inquiry concerning this communication should be directed to Dr. Anthony C. Caputa, whose telephone number is 703-308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is 703-308-0196.

Papers related to this application may be submitted to Group 1806 by facsimile transmission. Papers should be faxed to Group 1806 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-305-7939.

Anthony C. Caputa, Ph.D.

October 29, 1995

ANTHONY C. CAPUTA
PATENT EXAMINER
GROUP 1800